The relevance to medical science of doctors' self-challenge experiments with pathogens or infectious agents: 1767-2022

Bernard John Brabin[1, 2], *Loretta Brabin*[3]

[1]Liverpool School of Tropical Medicine, and Institute of Infection and Global Health, University of Liverpool, UK; [2]Global Child Health Group, Academic Medical Centre, University of Amsterdam, The Netherlands; [3]Division of Population Health Services Research and Primary Care, University of Manchester, UK

Abstract. Self-experimentation by medical doctors was a well-recognized research practice during the 18th and 19th centuries. This paper explores its contribution to the development of medical and public health practices by comprehensively collating, chronologically and by pathogenic group, reports of self-experimentation with infectious material and pathogens between the years 1767 and 2022. Tabulation of these events, which focuses primarily on physicians, provides a basis for understanding how the purpose of self-experimentation changed as medical knowledge developed. Reports are tabulated by year of experiment, country, investigator, experimental method, and clinical outcome. 43 self-challenge studies were conducted pre-1874 before proof of the germ theory of disease was accepted, mainly to investigate contagion. Results were often conflicting and anti-contagion views hindered acceptance of quarantine measures for yellow fever, cholera, and plague. Post-1874, 140 self-experiments took place, 17 with different parasites, 27 with different bacterial pathogens, and nine with different viruses or infectious agents, with peak frequency between 1891-1900. When specific agents of disease were known, anti-contagion theory was challenged, and experimental evidence used to explain clinical and disease patterns. Early study designs were limited as host immunity was not well understood. The reasons for putting oneself at great risk varied, although doctors were expected to set an example. Gradually their personal involvement declined in favour of consented volunteers, and reliance on a sample size of one became unacceptable.

Key words: self-challenge, self-experiment, pathogens, infections, doctors

Introduction

Before the mid-nineteenth century medical doctors interpreted illnesses caused by infectious pathogens as primarily non-contagious in nature, and treatments were based mostly on mistaken theories of disease pathogenesis (1). Prior to 1870, increasing acceptance of germ theory and lack of an experimental basis for disease causation may have motivated some doctors to self-experiment with infected matter, to assess the uncertain risk of contagion, including from bodily fluids. Opportunities were mainly pursued by individuals, and mostly involved single or multiple inoculations, or skin exposure to patient's vomit, pus, sputum, bodily discharges, blood and clothes - for instance, ingestion of cholera or plague vomit. Although the form of these experiments changed over time their purpose was to interpret results primarily in relation to the theory of non-contagion. Worthwhile questions arise on the reliability of such early clinical experiences, not least the fact that self-experimentation could not discriminate disease causation if more than one pathogen was involved. Such was the case of John Hunter's confusion of gonorrhoea and syphilis (2). While there might be academic and moral arguments for exposing oneself first, and such personal knowledge could be valuable for making reasonable inferences (3), without a wider grasp of the microbiological nature of contagious diseases,

study designs were limited, and misleading conclusions often drawn. One such instance was the conflicting recommendations for use of quarantine in seaports for ships carrying cholera or yellow fever passengers, indicating uncertainty as to whether these were contracted by direct contact (contagion), or some other means. The epidemiological confusion between the meaning of the terms contagious and infectious in the early nineteenth century is an illustration of this difficulty (4).

By 1875 the profile, value and utility of self-experimentation changed completely, triggered by key events. Casimir-Joseph Davaine (1812-1882) identified anthrax bacilli in sheep's blood in 1850 and published the results, together with the French pathologist physician Pierre Francois Olive Rayer (1793-1867) (5). This initial finding was a springboard from which to challenge non-contagion theories. Otto Obermeier (1843-1873) observed by microscopy the agent of louse-borne relapsing fever in human blood. His inability to reproduce the disease in animal models (and indeed himself) delayed publication of this finding until 1873 (6). Subsequently *Bacillus anthracis* was the first bacterium discovered by Robert Koch (1843-1910) in 1877, which he successfully cultured in aqueous humour. In 1878 Louis Pasteur (1822-1895) presented a seminal communication to the French Academy of Sciences, in a paper co-written with Jules Joubert (1834-1910) and Charles Chamberland (1851-1908), titled 'Germ theory and its Application to Modern Medicine and Surgery' (7). Pasteur had also taken up investigation of anthrax in 1877. In Scotland Joseph Lister (1827-1912) worked tirelessly on bacteriological work between 1870-1874. He corresponded with Pasteur in 1874 on germ theory and fermentative changes, noting parallels with the success of surgeons in reducing wound infection risk following amputation compared to the very high mortality (76%) for the same operation during the 1870 Franco-Prussian war (8, 9).

Although some physicians remained opposed to germ theory (1, 10), despite the discovery of the bacillus of cholera in 1854 by Filippo Pacini (1812-1883), gradually a medical community emerged which grasped the bacteriological model of infection (11,12). By 1890 fourteen diseases were identified, and recognized, as caused by specific bacterial pathogens (*Borrelia recurrentis*, relapsing fever 1873; *Bacillus anthracis*, anthrax, 1877; *Staphylococcus aureus*, suppuration, 1878; *Neisseria gonorrhoeae*, gonorrhoea 1879; *Salmonella typhi*, typhoid fever, 1880; *Mycobacterium tuberculosis*, tuberculosis, 1882; *Vibrio cholerae*, cholera, 1884 (although previously identified in 1854); *Corynebacterium diptheriae*, diptheria 1884; *Escherichia coli*, diarrhoea 1885; *Streptococcus pneumoniae*, pneumonia 1886; *Neisseria meningitidis*, meningitis 1887; *Brucella melitensis*, brucellosis, 1887; *Salmonella enteritidis*, food poisoning 1888; *Clostridium tetani, tetanus* 1889). Lister's papers in several issues of the Lancet from 1867 onwards reported the value of antisepsis in keeping the skin free from inflammation (13). Excitement from these discoveries encouraged self-experimentation with infectious pathogens as it promised rapidly acquired knowledge, harmonization of practice, and possibly fame. Ethical doubts were rudimentary, and with a sample size of one, self-challenges remained case reports. Despite these limitations, doctors continued to be viewed as appropriate primary volunteers for self-experiments. Subsequently this practice was not precluded by the Nuremburg Code of 1947. Elsie Widdowson (1906-2000) as late as 1958 endorsed this view stating: 'it was very desirable that the investigator should act as their own experimental subject, and not be prepared to do to others what they would not be prepared to do to themselves (14).'

This analysis collates for the first time both chronologically and by pathogenic group all reported self-experimentation with infectious material and pathogens by medical staff, primarily physicians, between 1767 and 2022. Pre-1874 experiments, before the proof of the germ theory of disease and involving unknown pathogens, are separately delineated. Their nature, outcomes and consequences are compared with medical self-experimentation after this period, which mostly involved known infectious agents. The implications of these self-experiments are discussed in relation to the historical development of microbiology, disease pathogenesis and causation, concepts of pathogen transmission, and ethical implications. The increase in the number of self-experiments with infectious agents by doctors in the nineteenth century following proof of the microbial causes of infection is estimated, and the reasons considered for their subsequent decline in the twentieth century.

Methods

Physical searches used library resources, and inter-library loan facilities. For recent publications electronic databases were examined including PubMed, Scopus, and ISI Web of knowledge, using the search terms: self-challenge, self-experimentation, self-infection, self-inoculation, anti-contagionism, human challenge, and specific pathogen names. Reference lists from general medical and historical journals were searched, and texts on the history of microbiology. Key sources were Arsen Fik's (1930-2001) listings of self-experimenters (15), which provided information from the Russian literature, and stated if investigators were medical doctors, and Lawrence Altman's (1937-) outline on human self-experimentation, which included oral histories of some 20th century medical investigators (16). A self-challenge/experiment or exposure is defined as: intentional exposure of the medical investigator to a patient with the medical condition, their bodily substances, or one or more specific pathogens, infectious agents, or potentially infectious vectors. Tabulations are presented by investigator, country of experiment, year of exposure, grouped by disease or pathogen studied, experimental method, and clinical outcome. Investigators who were not MDs are stated. Exposed individuals are assumed to have recovered, unless otherwise stated. Known deaths are listed. For undated experiments the publication year of the report describing the experiment(s) is used as the year of self-exposure. Excluded are accidental exposures. Self-challenge studies after 1873 are grouped by specific parasitic, bacterial, or viral pathogens. 1873 corresponded to the date of the report documenting the first discovery and identification of a specific pathogen causing a human infection (louse-borne relapsing fever due to *Borrelia recurrentis*) (6).

Doctors' self-experimentation with infectious diseases from 1767 to 1873

In the hundred years between the 1770s and 1870s, opinions were divided on the nature of febrile illness and its possible contagiousness. Initially a primary motivation to self-experiment derived from opposing views on quarantine to control three epidemic diseases - cholera, plague and yellow fever, which also caused high mortality, especially in seaports. Trying to prove contagionism by doing self-experiments using bodily discharges and matter from affected patients was a plausible way to test hypotheses on transmissibility. Table 1 lists these early self-challenge experiments by physicians who focused on these three epidemic diseases (references 17-39). There were eight plague, eight yellow fever and five cholera experiments, leading to two plague and one cholera death (15, 19). Yet almost all attempts failed to produce disease, strengthening the consensus for anti-contagionism (1), as well as the lack of need for quarantine, which was very unpopular. Nicolas Chervin (1783-1843), who was a major anti-contagionist, drank large amounts of a yellow fever patient's black vomit without ill effect (28). His report led to quarantine laws being stopped (1828) by the French Academy, an influential body that also informed approaches to cholera and plague. In all the self-experiments with yellow fever for which the clinical outcome was reported, none had ill effects (Table 1). Anti-contagionist views were further endorsed by three self-experiments by French physicians, who remained well following exposures (17,18) (Table 1). A United Kingdom report in 1849 opposed cholera quarantine. In 1835 Antoine Barthélémy Clot (1793-1868) inoculated his cut skin with pus from a plague patient and put the patient's blood on a bandage over the wound (21, 22). He remained well and was a strong opponent of the contagion theory for plague. His influence on others was considerable and England and Australia abolished plague quarantines in 1841. Absence of plague epidemics after 1845 limited interest in further self-challenge studies. While the initial change from anti-contagionism to contagionism preceded the decisive discoveries of Pasteur and Koch, by the mid-1870s most physicians were forced into the contagionist camp (12). Morbidity also decreased thanks to the sanitary measures sometimes introduced by the anticontagionists.

Such views were also strengthened by empirical research, such as that of Charles Maclean (c1766-1824), who, in his 1817 book, argued that quarantines do not work and may even cause enormous harm (40). For diseases which require a vector for transmission his

Table 1. Self-experimentation with pathogenic material by doctors between 1767 and 1873 [a].

Investigator	Country	Year	Disease	Self-experiment	Outcome	Reference
Francois Foy (1793-1867)	France	1831	Cholera	Breathed air, tasted vomit, and inoculated blood of patient who died of cholera	Remained well	17, 18
Scipion Pinel (1795-1859)	France	1831	Cholera	Breathed air, tasted vomit, and inoculated blood of patient who died of cholera	Remained well	17, 18
Wayrot	Unknown	1831	Cholera	Inoculated with blood of patient who died of cholera	Remained well	17, cited by 1
Jean-Louis Guyon (1794-1870)	France	?	Cholera	Details unreported	Survived	17, cited by 1
Otto Hugo Franz Obermaier (1843-1873)	Germany	1873	Cholera	Self-injection of cholera vaccine he prepared	Died after vaccination	15
Danilo Samoilovich (1744-1805)	Russia	1771	Plague	Wore disinfected cloths of plague patient	Remained well	15
Matvei A Dagio	Russia	1772	Plague	Self-inoculated his skin with matter from a plague patient	Unwell; survived	15
Nicolas Réné Dufriche-Desgenettes (1762-1837)	France	1798	Plague	Self-inoculation	Survived	1, 15
Anthony White (1782-1849)	Egypt	1802	Plague	Rubbed discharge from a suppurating thigh gland on to skin and cut	Died after 8 days	19, cited by 1
Eusebio Valli (1755-1816)	Italy	1803	Plague	Self-infection from smallpox pustules and from plague simultaneously; died later of yellow fever;	Survived	15, 20
Alois Rosenfield (b 1816)	Turkey	1816	Plague	Consumed dried lymph glands and bone material of plague cases; rubbed skin with plague boil material	Died from plague	15
Arsene Francois Bulard (1827-1876)	Egypt	1834	Plague	Wore for 48 hours shirt from plague patient which was soaked in patient's blood	Remained well	15
Antoine Barthélémy Clot (1793-1868)	France	1835	Plague	Inoculated his cut skin with pus from a plague patient and put patient's blood on bandage over the wound	Remained well	21, 22
Nathaniel Potter (1770-1843)	USA	1798	Yellow fever	Scratched sweat, and inoculated pus from abscess of dying yellow fever patient	No ill effects	15
Stubbins Firth (1784-1820)	USA	1802	Yellow fever	Slept with cases; ingested, and exposed eyes and skin to vomit, saliva, urine; injected their blood into vein	Remained well	23
Isaac Cathrall (1764-1819)	USA	1800	Yellow fever	Repeatedly ingested or tasted patient's black vomit	No ill effect	24, cited by 1

Investigator	Country	Year	Disease	Self-experiment	Outcome	Reference
Jean-Louis Guyon (1794-1870)	France	1822	Yellow fever	Wore shirt of yellow fever patient; rubbed their black vomit into skin and drank it	Unknown	15, 25, 26,
Samuel Musgrave (b 1732)	USA	?	Yellow fever	Details unreported	Unknown	27, cited by 1
Nicolas Chervin (1783-1843)	France	1816	Yellow fever	Drank large amounts of patient's black vomit	No ill effect	28, cited by 1
P.A.P. Prost (1724-1796)	France	~1821	Yellow fever	Details unreported	Unknown	28, cited by 1
John D. Dorsey (b 1783)	USA	?	Yellow fever	Details unreported	Unknown	28, cited by 1
Jean-Baptiste Émile Widal (1825-1893)	France	1873	Herpes	Re-inoculated fluid from his own herpetic sore into different area of his skin	New lesions occurred	29
Robert Remak (1815-1865)	Germany	1842	Favus	Self-inoculated crusts of fungal skin infection (*Trichophyton schoenleinii*).	Produced skin lesion	27
John Hunter (1728-1793)	UK	1767	Syphilis	Scarified penis with pus of patient with gonorrhoea, and probably syphilis; later died from syphilis	Penile chancre & adenopathy.	30
Benjamin Bell (1749-1806)	UK	1797	Syphilis	Introduced into urethra secretion of syphilitic chancre	Syphilis but not gonorrhoea	15
Alexandre Dubled (b 1800)	France	1824	Syphilis	Self-inoculated arm with pus from penile chancre and urethra	Uncertain	15
Paris students b	France	1829	Syphilis	Two students inoculated themselves with syphilis. following episode one committed suicide	One died	19, cited by 1
Philippe Ricord (1800-1889)	France	1849?	Syphilis	Self-inoculation of thigh with pus from syphilitic patient's lesion	Unrecorded	31
Robert Ritter von Welz (1814-1878)	Germany	1849	Syphilis	Inoculated himself with pus from chancre of infected monkey	Ulcer at inoculation site	32, 33
Lindemann	France	1851	Syphilis	Inoculated hands with secretions from syphilitic ulcers, under auspices of Medical Academy of Paris	Developed syphilis; died	15
Joseph von Lindwurm (1824-1874)	Germany	1851	Syphilis	Repeated exposures with matter from human syphilitic ulcers	Later died from syphilis	32, 34
Joseph-Alexandre Auzias-Turenne (1812-1870)	France	?	Syphilis	At his death in 1870 his skin was covered in scars from attempts at syphilisation with infected matter	Unrecorded	35
Franz von Rinecker (1811-1883)	Germany	?	Syphilis	Self-inoculation with material from syphilitic infant	Developed syphilis	15

Table 1 continues

Table 1. Self-experimentation with pathogenic material by doctors between 1767 and 1873 [a]. *(continued)*

Investigator	Country	Year	Disease	Self-experiment	Outcome	Reference
Borgioni	Italy	1862 ?	Syphilis	Self-inoculation with syphilitic patient's blood	Syphilis after two months	15
Louis Valentin (1758-1829)	France	?	Gonorrhoea	Self-inoculation of urethra with gonorrhoeal pus	Uncertain	15
Désiré Guyomar	France	1858	Gonorrhoea	Self-inoculation into urethra of pus from a granular opthalmia neonatorum	Severe urethritis	15
Stepan Semionovich Andreevskii (1760-1818)	Russia	?	Anthrax	Self-infection with anthrax	Critically ill, but survived	15
Arnold Trousseau (1801-1867)	France	1829	Diptheria	Punctured his tonsils and arm with a lancet scraped on a diptheritic membrane	Small blister on arm	32, 36
Michel Peter (1824-1893)	France	1830?	Diptheria	Punctured lip with diptheritic membrane and painted throat with fluid from membrane	No adverse effects	32, 37
Daniel Cornelius Danielson (1815-1894)	Norway	1844-6 1857-8	Leprosy	Self-injection of leprous nodules, blood, pleural fluid; included nurses, assistants, and syphilitic patient	Lesions healed	15, 38
Giuseppe Profeta (1840-1910)	Italy	~1870	Leprosy	Repeated inoculations with material from leper's skin and injection of leper's blood	No leprosy; mild response	15
Ferdinand Ritter von Hebra (1816-1880)	Austria	?	Scabies	Self-infected skin with itch mites	Scabies	15
David Gruby (1810-1906)	France	1841	Ringworm	Self-inoculation with crusts of patient's *tinea favus* skin infection	Local inflammation	39

Notes: a: for each specific disease self-experiments are listed chronologically by year of experiment; absence of lifespan indicates dates unavailable; b: medical students.

conclusion was correct, although he was unaware of the role of vector transmission. The empirical approach detracted from reliance on self-experimentation. For yellow fever, he based his reasoning on a very thorough analysis of outbreaks in Spain. He was one of the earliest epidemiologists and his conclusions set an anti-contagionist backdrop for later discussions on cholera and plague, with further evidence from three European cholera pandemics in the nineteenth century (1817;1831;1846-1849). Yet John Snow's (1813-1858) epidemiological analyses of the 1854 London outbreak provided clear evidence against the anti-contagionists, and by 1869 even Rudolf Virchow (1821-1902), a well-known anti-contagionist, admitted an organism was responsible and by 1884 accepted quarantine might be effective (41). A motivation for better epidemiological analysis was being established.

In this period, self-experiments were also conducted for common diseases: eleven syphilis, two gonorrhoea, one anthrax, two diptheria, two leprosy, and one for ringworm (15, 19, 30-39). Their motivation was probably more to further medical knowledge and improve clinical practice. Most self-experiments concerned syphilis and resulted in three deaths (Table 1). The earliest, reported in Table 1, is that of John Hunter (1728-1793), who in 1767 probably scarified himself

with pus of a patient with gonorrhoea, who may also have had syphilis, and which led to a penile chancre and inguinal adenopathy. The aortic aneurysm identified at Hunter's death was possibly of syphilitic origin (30). The momentum for the largely French and other European physicians to undertake these experiments during the nineteenth century was influenced firstly, by confusion as to whether syphilis was only a human disease, and secondly, whether repeated inoculation with syphilitic matter would induce immunity. A celebrated debate between Philippe Ricord (1800-1889), who self-inoculated with syphilitic pus around 1849, and Joseph-Alexandre Auzias-Turenne (1812-1870), who had tried to infect monkeys, centred on Ricord's view that syphilis was a distinctly human disease. Ricord taunted Auzias-Turenne suggesting having 'the courage of one's own convictions …[and] inoculate himself with pus from one of his monkey's ulcers and wait for the appearance of symptoms' (35, 42). Auzias-Turenne took the criticism to heart and at his death in 1870 his skin was covered in scars from attempts at his own syphilisation, attempting to induce immunity, using infected matter of syphilis patients (43). Before the advent of the bacteriological revolution syphilisation reflected what doctors thought about the aetiology and pathology of syphilis, as well as potential therapeutic options, such as inoculation, for their patients.

Self-experimentation by doctors with parasite pathogens after 1873

Thirty self-experiments between 1873 and 1989 with intended parasite exposure by twenty-seven investigators are listed in Table 2 (references 32, 44-55). Nearly all were conducted by physicians, with one medical student (Patrick Thurbern Manson), one veterinarian (Fritz Huber), and one entomologist (Kenneth Mellanby). The profession of two is uncertain (Margarita Alekseeva and Gertrud Vollmer). The most frequent locations were Russia and Italy, and in contrast to the pre-1873 self-experiments, none were conducted in France. One, which was probably voluntarily acquired, resulted in death from amoebiasis (Fritz Schaudinn) (32). They variously addressed differences between what caused the disease, stages of parasite life cycles, or how the parasite was transmitted. The initial self-experiment with the parasite helminth *Ancyclostoma duodenale* (hookworm) was conducted by the Italian physician and zoologist Giovanni Grassi (1854-1925) in 1878 resulting in no infection (46). It was then not until 1922, when, in a self-experiment in Japan by Shimesu Koino, that this parasite's life cycle was elucidated with the demonstration of hookworm larva in his sputum (45). Grassi conducted further self-experiments in 1879, using the roundworm *Ascaris lumbricoides* resulting in excretion of its eggs in his faeces (32, 44). Again between 1896 and 1900 he exposed himself to mosquitoes which were thought to be carrying the *Plasmodium falciparum* malaria parasite (15). He remained uninfected.

Four investigators listed in Table 2 are known to have conducted multiple self-experiments with parasitic pathogens: Arthur Loos (1862-1923) in Egypt in 1898 with hookworm (32), and in the same year with a second helminth *Strongyloides stercoralis* (15, 48*)*. Fritz Schaudinn (1871-1906) in Germany with different protozoan amoeba species which resulted in 1906 in his death from complications from an amoebic abscess (32); Claude Barlow (1876-1969) in 1920 in China with Fasciolopsis (54), and again in the same investigator, in 1944 in Egypt with schistosomes, both of which led to faecal egg detection (16, 55); Salvatore Calandruccio (1858-1908), who from 1881 onwards self-experimented with many parasites (32). Calandruccio holds the record for undertaking the most self-experiments. Ostensibly there was no protozoan or helminth harmful to man present in Sicily, that he either did not ingest voluntarily, in the form of cysts, eggs, or larvae, or self-administered by injection and survived. These included: amoebae, *Giardia duodenalis, Balantiidium coli,* plasmodia of malaria, human and canine ascarids, *Enterobius vermicularis*, *Strongyloides stercoralis, Echinococcus granulosus, Taenia solium* and *saginata, Hymenolepis nana*, and even an Acanthocephalan such as *Moniliformis moniliformis*, which damages the human intestine (56). The collaboration between the Italian multiple self-experimenters Grassi and Calandruccio eventually led to disputes as to whose observations were first reported, which became irreconcilable (57).

Table 2. Self-experimentation by doctors with parasite pathogens between 1874-2022a.

Medical investigator	Country	Year	Pathogen	Self-Experiment	Outcome	Ref
Giovanni Battista Grassi (1854-1925)	Italy	1879	*Ascaris lumbricoides*	Swallowed 100 embryonated eggs	Ascaris eggs in faeces	32, 44
Salvatore Calandruccio (1858-1908)	Italy	~1881	*Ascaris lumbricoides*	Swallowed large number of embryonated *A. lumbricoides* eggs	No infection	32
Sado Yoshida (1878-1964)	Japan	1918	*Ascaris lumbricoides*	Swallowed *A. lumbricoides* larva recovered from infected guinea pig lungs	Ascaris eggs in faeces	32
Shimesu Koino	Japan	1922	*Ascaris lumbricoides*	Swallowed 2000 *A. lumbricoides* eggs	Sputum larva; faecal worms	45
Giovanni Battista Grassi (1854-1925)	Italy	1878	*Ancylostoma duodenale*	Swallowed 100 *A. duodenale* eggs	No infection	46
Arthur Edwin Boycott (1877-1938)	England	1903	*Ancylostoma duodenale*	Smeared larval cultures on arm. No initial infection, but by 1911 reported positive results	No infection	47
Arthur Looss (1862-1923)	Egypt	1898	*Ancylostoma duodenale*	Smeared larva on skin	Skin swollen & faecal eggs	32
Charles Bentley (1878-1949)	India	~1900	*Ancylostoma ceylanium*	Smeared 1200 larva on arms	Abdominal colic	32
Arthur Looss b (1862-1923)	Egypt	1898	*Strongyloides stercoralis*	Swallowed strongyloides larva	No eggs of strongyloides	48
Fritz Schaudinn (1871-1906)	Germany	Undated 1906	*Entamoeba coli* *Entamoeba histolytica*	Self-infection Probably voluntarily acquired infection during research on amoeba	No illness Amoebic abscess; died	32
Carl Jacob Christian A. Gerhardt (1833-1920)	Germany	1884	*Plasmodium* (? species)	Injected blood of patient with clinical malaria	Clinical malaria	15
Nikolai A. Sakharov (1852-1927)	Russia	1890	*Plasmodium* (? Species)	Self-injection of leech's intestinal contents which four days before had been attached to a malaria patient	Clinical malaria	15
Louis Appia (1818-1898)	India	1896	*Plasmodium* (? species)	Self-exposed to mosquitoes that had recently bitten a malaria patient	Remained well	15
Ronald Ross (1857-1932)	India	1896	*Plasmodium falciparum*	Twice ingested 'psorosperm' cells from gut of presumed infected mosquitos	No infection	49
Wilhelm W. SchÜffner (1867-1949)	Sumatra & Holland	1898 & 1928	*Plasmodium malariae*	Self-exposed to bites of mosquitoes infected with *P. malariae*	Developed malaria	15
Giovanni Battista Grassi (1854-1925)	Italy	1896 -1900	*Plasmodium falciparum*	Self-exposed to mosquitoes collected in hospital, and those which developed from larva of infected mosquitoes	Remained well	15

Medical investigator	Country	Year	Pathogen	Self-Experiment	Outcome	Ref
Patrick Thurbern Manson c (1878-1902)	England	1900	*Plasmodium vivax*	Patrick Manson's son was exposed in London to infected Anopheline mosquitoes which were transported from Italy	Developed tertian malaria	50
George Carmichael Low (1872-1952)	Italy	1900	*Plasmodium falciparum*	Intentionally lived in mosquito-proof house in worst malaria endemic area of Italy	Remained well	15
V.V. Favr (1874-1920)	Russia	1901	*Plasmodium* (? species)	Self-exposed to infected Anopheline mosquitoes	Developed malaria	15
Margarita I. Alekseeva	Russia	Undated	*Plasmodium falciparum*	Self-exposed to infected Anopheline mosquitoes	Developed tertian malaria	15
Gertrud Vollmer	Germany	Undated	*Plasmodium* (? species)	Self-exposed to infected Anopheline mosquito	Developed tertian malaria	15
David Clyde (1925-2002)	USA	1974-76	*Plasmodium falciparum*	Self-exposed to non-irradiated & irradiated infected mosquitos. Contracted falciparum and vivax infections	Clinical malaria	32, 51
James Frederick Corson (b 1878)	Tanganyika	1912-14	*Trypanosoma brucei & rhodesiense*	Allowed bites from tsetse flies with *T. brucei,* and injection of blood of guinea pigs with *T. rhodesiense*	Unknown	15
Maz Taute (1878–1934)	Mozambique	1912-15	*Trypanosoma brucei*	Allowed bites of tsetse flies infected with *T. brucei;* injected himself with blood from dog sick with trypanosomiasis	No infection	15, 52
Fritz Huber (b 1914)	Mozambique	1912-15	*Trypanosoma brucei*	Allowed bites of tsetse flies infected with *T. brucei;* injected himself with blood from dog sick with trypanosomiasis	No infection	15, 53
Claude Herman Barlow (1876-1969)	China Egypt	1920 1944	*Fasciolopsis buski* *Schistosoma haematobium*	Swallowed parasite adult flukes Applied schistosome larva to skin four times in three weeks	Fasciolopsis faecal eggs Symptoms & urine eggs	54 16, 55
V.S.Kirchek	Russia	1989	*Taenia saginata*	Investigator swallowed larva of reindeer tapeworm	Heart & blood abnormalities	15
Eugenii Ivanovich Martinovskii (1874-1934)	Russia	1904	*Leishmania tropica*	Introduced matter from patient's ulcer into small arm burns and re-inoculated samples from first injection site	Cutaneous leishmaniasis	15
Kenneth Mellanby d (1908-1993)	UK	1939-44	*Sarcoptes scabiei*	Self-inoculation with trial vaccines	No efficacy	15
Jay Frank Schamberg (1870-1934)	USA	1909	*Pediculoides ventricosus*	Self-infection with *P. ventricosus* to establish as a cause of urticaroid dermatitis	Dermatitis	15

Notes: a: for each specific parasite category self-experiments are listed chronologically by year of experiment. absence of lifespan indicates dates unavailable; b: parasitologist; c: medical student; d: medical entomologist.

Ten of the twelve experiments with malaria involved voluntary exposure to malaria infected mosquitoes, and two investigators used injections with infected blood — Carl Jacob Christian Gerhardt (1833-1920) with a patient's blood, and Nikolai Sakharov (1852-1927) with leech's intestinal contents (15) (Table 2). The blood injections tested malaria causation, and mosquito exposures vector transmission. In 1896 Ronald Ross (1857-1932) ingested twice 'psorosperm' cells obtained from mosquito gut, which he mistakenly thought were malaria organisms which could be transmitted by drinking infected water (49). Later, and after he discovered the correct mode of infection in 1898, he considered delays from military redeployment had prevented him from identifying the malaria cycle sooner by allowing him to infect healthy men 'beginning with himself ' (49). Eight of the investigators developed clinical malaria and all recovered. Three species of human malaria parasites were tested. All experiments were conducted between 1884-1901, except those for David Clyde (1925-2002), who between 1974-76 self-exposed himself to both irradiated and non-irradiated infected mosquitoes in what was the latest malaria self-experiment by a doctor. He also carried out self-challenges with antimalarial drugs (32, 51). In Tanzania between 1912-14 vector exposure using infected tsetse flies was also used to investigate trypanosome transmission, with no adverse outcomes being reported (15, 52, 53).

Isolated single self-experiments were done with schistosome and taenia larva, as well as exposures to leishmania, flukes, and ecto-parasites, mostly with demonstrable clinical consequences for the investigators, but no fatalities (14) (Table 2).

Self-experimentation by doctors with bacterial pathogens after 1873

Eighty-two self-experiments, with twenty different bacterial species, in studies across twenty-three countries were undertaken between 1874 and 1987 (Table 3) (references 58-83). Only two investigators self- experimented twice: Elie Metchnikoff (1845-1916) (16, 75), and Waldemar Haffkine (1860-1930) (15, 70), both self-challenged with *Vibrio cholera* in 1892. Previously Metchnikoff in 1881 made a near suicidal attempt using the blood of a patient with relapsing fever (*Borrelia recurrentis*), and Haffkine in 1897 self-injected with an attenuated plague (*Yersinia pestis*) vaccine. In 1899 Lord Joseph Lister, President of the Royal Society, characterized Haffkine as an honourable man for making himself the first person to receive the cholera vaccine and putting his life at risk in his work against cholera and plague (84). Haffkine's successes against cholera and plague opened the door to wider acceptance of vaccines for bacterial diseases (84). Two individuals died: Arthur Bacot (1866 -1922), a medical entomologist, succumbed to typhus (*Rickettsiae prowazeckkii*) after allowing multiple lice from a public bathhouse to repeatedly bite him (15). Daniel Carrion (1857-1885), a Peruvian medical student, inoculated himself with blood lanced from the skin lesion of a patient with *verruga peruana*, and died from Oroya fever, which ultimately proved the two conditions were caused by the same agent (*Bartonella bacilliformis*) (58, 59). Incredibly a second Peruvian doctor, Maxine Kuczynski-Godard (1890-1967) repeated the same self-experiment in 1937. He developed Oroya fever, but survived, despite the absence of antibiotics (60), (Table 3).

After 1873 most self-experiments were conducted by doctors with bacteria: nine for plague, eight for relapsing fever, eleven for typhus and ten with *Staphyloccocus aureus*. Initially this effort was directed to establish causation, but from the early twentieth century onwards, with pathogenic causes identified, many self-experiments focused on vaccine testing and development (85). Others listed in Table 3 were directed more to confirming evidence of causation, or to clarify clinical aspects related to pathogenesis. Several personal stories of discovery during this period have been described (16), including some famous bacterial auto-experiments. A very notable controversy was sparked between Robert Koch (1843-1910) and Max von Pettenkofer (1818-1901) on the utility of quarantine for cholera cases. In 1892 Pettenkofer swallowed infected broth culture containing cholera bacilli to demonstrate (in opposition to Koch), his view that the bacillus alone was insufficient to cause serious disease (72) (Table 2). His students offered to

Table 3. Self-experimentation by doctors with bacterial pathogens between 1874 – 2022 a.

Medical investigator	Country	Year	Pathogen	Self-Experiment	Outcome	Ref
Daniel Alcides Carrión (1857-1885)	Peru	1885	*Bartonella bacilliformis*	Inoculated blood lanced from skin of verruga peruana lesion	Died from Oroya fever	58, 59
Máxime Kuczyński-Godard (1890-1967)	Peru	1937	*Bartonella bacilliformis*	Injected into skin *B. bacilliformis* cultures	Oroya fever	60
Armauer Hansen (1841-1912)	Norway	1879	*Mycobacterium leprae*	Tried to infect himself. Also, injected conjunctival nodular leprosy tissue into two (unconsented) leprosy patients	No infection	32
Socrates Lagoudaky (1863-1944)	Egypt	1934	*Mycobacterium leprae*	Self-injection of blood from leprous patient, intramuscular and intravenous. Also injected Dr Carly Seyfarth (b 1890)	Developed leprosy	15
Georgii N. Gabrichevskii (1860-1907)	Russia	1904	*Streptococcus pyogenes*	Self-injected experimental vaccine containing streptococcal broth culture, and to two children	Vaccine was effective	15
Carl Garré (1857-1928)	Switzerland	1883	*Staphyloccocus aureus*	Scratched skin and nail bed with *S. aureus* from bone abscess. Proved that it causes carbuncles and boils	Skin abscess & adenopathy	15, 32
Ernst Bumm (1858-1925)	Germany	1885	*Staphyloccocus aureus*	Subcutaneous injection of staphylococci from a breast abscess	Developed skin abscesses	61
Max Bockhart (b 1858)	Germany	1886	*Staphyloccocus aureus*	Repeated subcutaneous inoculations of staphylococci from a patient	Skin pustules which healed	62
Marshall A. Barber (1868-1953)	Philippines	1913	*Staphyloccocus aureus*	Drank milk containing *S. aureus* kept at room temperature	Strong enteric symptoms	63
Gail Monroe Dack (1901-1976)	USA	1930	*Staphyloccocus aureus*	Ingested cake spoiled by staphylococci	Clinical food poisoning	15
Claude Ernest Dolman (1906-1994)	Canada	1931-43	*Staphyloccocus aureus*	Several trials when swallowed or injected various preparations of staphylococcal toxin	Clinical food poisoning	15, 16 p185
Stephen Dyonis Elek (1914-1992)	England	1956	*Staphyloccocus aureus*	Sub-cutaneous injections of increasing concentrations to one million staphylococci	Skin pustules at higher doses	64
Patrick E. Conen (b 1928)	England	1957	*Staphyloccocus aureus*	Sub-cutaneous injections of increasing staphylococci concentrations. Participated with Elek	Skin pustules at higher doses	65
Richard V. McCloskey (1933-2018)	USA	1973	*Staphyloccocus aureus*	Self-inoculation of staphylococcal solution of bacteria into forearm	Toxic reaction, swollen arm	66

Table 3 continues

Table 3. Self-experimentation by doctors with bacterial pathogens between 1874 – 2022 a. *(continued)*

Medical investigator	Country	Year	Pathogen	Self-Experiment	Outcome	Ref
George Miller Sternberg (1838-1915)	USA	1882-84	*Neisseria gonorrhoea*	Twice inserted cotton soaked in gonococcal bacterial culture into urethra	No adverse outcome	15, 32
Ernst Werheim (1864-1920)	Austria	1890-91	*Neisseria gonorrhoea*	Self-injection with pure culture of *N. gonorrhoea* from case of salpingitis	Gonorrhoea	15
E. Boreau	France	~1893	*Neisseria gonorrhoea*	Urethral inoculation of pus from virulent gonorrhoeal urethritis case; mercury treatment after 11 hours	No adverse outcome	15
Paul Maissoneuve (1849-1927)	France	1906	*Treponema pallidum*	Inoculation of syphilitic material into skin scratches, which were smeared with mercury one hour later	No adverse outcome	15
Hideyo Noguchi (1876-1928)	USA	1911	*Treponema pallidum*	Cutaneous injection of phenolised extract of *T. pallidum* (luetin)	Syphilis in 1913	67
Francisco León y Blanco	Mexico	1939	*Treponema carateum*	Self-infection with *T. carateum*	Reproduced skin disease of pinta	68
Egon Tomasczewski (1874-1922)	Germany	1902	*Haemophilus ducreyi*	Self-infected with material from patient's soft chancre	Contracted infection	15
Alexandre Emile John Yersin (1863-1943)	France	Undated	*Yersinia pestis*	Self-inoculation with live attenuated plague vaccine	Remained well	15
Waldemar Mordecai Wolff Haffkine (1860-1930)	India	1897	*Yersinia pestis*	Self-injection with triple the normal dose of his devitalised anti-plague vaccine	High fever, local pain, headache	15
Richard Pearson Strong (1872-1948)	USA	1909	*Yersinia pestis*	Self-vaccinated using plague vaccine	Uncertain	15
Magdalena Petrovna Pokrovskaia (b1901)	Russia	~1930	*Yersinia pestis*	Self-subcutaneous injection of large quantity of cultured live plague bacteria and vaccine inhalation	General reaction	15
L.Otten (b 1877)	Germany	~1934	*Yersinia pestis*	Two subcutaneous injections with virulent live plague vaccine (~ one billion bacteria)	No side effects	69
N.K. Zav'ialova	Russia	~1948	*Yersinia pestis*	Intentionally induced primary pneumatic plague after prior accidental infection with pneumatic plague	Mild limited clinical illness	15
Vasililii Pavlovich Smirnov (1901-1976)	Russia	1950	*Yersinia pestis*	Effect of live subcutaneous plague vaccine; rubbed on leg wound splenic material of guinea pig who died of plague	Plague ulcer and fever	15

Medical investigator	Country	Year	Pathogen	Self-Experiment	Outcome	Ref
Evgeniia Ilinichna Korobkova	Russia	~1956	*Yersinia pestis*	Effect of live sensitised plague vaccine N46-S	No side effects	15
Nikolai N. Zhukov-Verezhnikov (1908-1973)	Russia	Undated	*Yersinia pestis*	Subcutaneous self-injection of plague vaccine M#74 using three billion plague bacteria	Safety demonstrated	15
Jaime Ferrán y Clua (1851-1929)	Spain	1885	*Vibrio cholerae*	Self-tested partially inactivated vaccine, and on thousands of people, virulent organisms survived leading to deaths	Survived	15
Waldemar Mordecai Wolff Haffkine (1860-1930)	France	1892	*Vibrio cholerae*	Two self-injections with attenuated and more virulent cholera bacteria as vaccine.	Febrile, local tenderness	15, 70
Ernest Hanbury Hankin (1865-1939)	France	1892	*Vibrio cholerae*	Self-injection with two varied strengths of Haffkine cholera vaccine	Febrile, local tenderness	71
Martz E	Russia	1892	*Vibrio cholerae*	Swallowed faecal samples from a cholera patient	Uncertain	15
Max von Pettenkofer (1818-1901)	Germany	1892	*Vibrio cholerae*	Swallowed infected broth culture of cholera bacilli	Mild cholera	72
Rudolf E. Emmerich (1852-1914)	Germany	1892	*Vibrio cholerae*	Swallowed broth culture of cholera bacilli developing more severe symptoms than patient who provided sample	Severe cholera	32, 73
Elie Metchnikoff (1845-1916)	France	1892	*Vibrio cholerae*	Swallowed V cholerae after alkalinisation of stomach	No symptoms	15, 74
Daniil Kirillovich Zabolotnyi (1866-1929)	Russia	1893	*Vibrio cholerae*	Swallowed inactivated *V. cholera,* followed by *V. cholera*, neutralising gastric juice with bicarbonate	Uncertain	15
Nikolai Fiodorovich Gamaleia (1859-1949)	Russia	1902-20	*Vibrio cholerae*	Injected with attenuated forms of cholera vaccine. His wife and several others participated	Survived but no details	15
Frédéric Albert Trensz (1901-1990))	Gabon	1926-27	*Vibrio gabunensis*	Isolated and drank a pure culture of *V. gabunensis* while at Lambarene, the missionary hospital of Albert Schweitzer	Dysentery	15, 75
Zinaida Vissarionovna Ermol'eva (1898-1974)	Russia	~1942	*Cholera-like vibrio*	Drank 1.5 billion cholera-like vibrios	Unwell but recovered	15
Osip Osipovich Mochutkovski (1845-1903)	Russia	~1876	*Borrelia recurrentis*	Injected himself with blood of patients infected with relapsing fever	Developed relapsing fever	15

Table 3 continues

Table 3. Self-experimentation by doctors with bacterial pathogens between 1874 – 2022 a. *(continued)*

Medical investigator	Country	Year	Pathogen	Self-Experiment	Outcome	Ref
Grigorii Nikolaevich Minkh (1836-1896)	Russia	~1875	*Borrelia recurrentis*	Scratched wrist with tube of blood of relapsing fever patient containing *B. recurrentis* spirochaetes	Developed relapsing fever	15
Elie Metchnikoff (1845-1916)	France	1880	*Borrelia recurrentis*	Suicidal attempt using blood of patient with relapsing fever	Severely ill	15, 74
Cuthbert Christy (1863-1932)	India	1900	*Borrelia recurrentis*	Repeatedly placed tick on relapsing fever patient's skin and then placed tick on own skin	Developed relapsing fever	15
Viacheslav Karlovich Stefanskii (1867-1949)	Russia	1915	*Borrelia recurrentis*	For ten weeks allowed bed bug bites wrongly thought to be infected with relapsing fever	Remained well	15
Nilolai Ivanovich Latyshev (1886-1951)	Russia	1926-27	*Borrelia recurrentis*	Allowed tick bites, and injected himself with blood of sick giant gerbil	Developed relapsing fever	15
N.N. Beshcheva-Strunina	Russia	1945	*Borrelia recurrentis*	Lice from relapsing fever patients allowed to feed on investigator	Three episodes relapsing fever	15
Henryk Mosing (1910-1999)	Poland	1945-50	*Borrelia recurrentis*	Scratched skin and infected it with crushed lice and their faeces	Uncertain	15
Barry Marshall (1851-)	Australia	1985	*Helicobacter pylori*	Swallowed suspension of one million cultured *H. pylori*	Minor gastric symptoms	76
Arthur Morris (1956-)	New Zealand	1987	*Helicobacter pylori*	Swallowed suspension of cultured *H. pylori*	Minor gastric symptoms, significant upper abdominal pain	77, 78
Almroth E Wright (1861-1947)	England	1899	*Brucella melitensis*	Following vaccination with killed vaccine voluntarily exposed himself to live brucella bacteria	Developed brucellosis	79
Etienne Burnet (1873-1960)	France	1921	*Brucella melitensis*	While recovering from brucellosis self-subcutaneous injection with live, or dead brucella as diagnostic test	Reaction to live bacteria	15
Andrei Iakovlevich Alymov (1893-1965)	Russia	1933	*Brucella melitensis*	Infected himself with brucellosis	Developed brucellosis	15
Nathan Ronald Brewer b (b 1904)	USA	1932-37	*Brucella melitensis*	Pharmacodynamic activity of fractions of brucella bacteria.	Developed brucellosis	15
James Carroll (1854-1907)	USA	1904	*Salmonella typhi*	Ingested oral typhoid vaccine which accidentally contained live bacteria	Remained well	16p370 80

Medical investigator	Country	Year	Pathogen	Self-Experiment	Outcome	Ref
Edward Bright Vedder (1878-1952)	USA	1904	*Salmonella typhi*	Ingested oral typhoid vaccine which accidentally contained live bacteria	Developed typhoid fever	16, 80
Harry Lorenzo Gilchrist (1870-1943)	USA	1904	*Salmonella typhi*	Ingested oral typhoid vaccine which accidentally contained live bacteria	Developed typhoid fever	16, 80
P.N.Triodin	Russia	1928	*Salmonella typhi*	Ingested oral dry typhoid vaccine and then drank a live culture of *S. typhi*	Mild enteric symptoms	15
Barnabas Rédley (b 1913)	Hungary	Undated	*Salmonella strains*	Ingested 20 varieties of *S. enterica*, as well as shigella bacterial strains	Fever and diarrhoea	15
Kiyoshi Shiga (1870-1957)	Japan	Undated	*Shigella*	Subcutaneous self-injection with culture of shigella bacteria	Abscess and fever	15
Osip Osipovich Mochutkovski (1845-1903)	Russia	1876	*Rickettsia prowazekkii*	Several attempts to inoculate himself with blood of a patient infected with typhus	Developed typhus	15, 32
N.A.Finn	Russia	1878	*Rickettsia prowazekkii*	Self-injection of blood from of a patient infected with typhus/typhoid	Uncertain	15
Charles Jules Henri Nicolle (1866-1936)	Tunisia	1916	*Rickettsia prowazekkii*	Self-brushed infected lice and sera from recovered typhus patients; when repeated on children they became infected	Remained well	15, 81
Heindrich Werner (b 1874)	Germany	1916	*Rickettsia prowazekkii*	Self-injection with soldier's blood with recurrent fever	Unwell after three weeks	15
Hélène Sparrow (1891-1970)	Poland	1921	*Rickettsia prowazekkii*	Self-injected emulsion from guinea pig abdominally infected with blood from a typhus patient	Mild typhus	15
Arthur W. Bacot c (1866-1922)	Poland	1922	*Rickettsia prowazekkii*	Large number of lice collected from public bathhouse allowed to bite investigator repeatedly	Died from typhus	15
Fiodor Gisbertovich Berngoff (d 1951)	Russia	1930	*Rickettsia prowazekkii*	Lice from typhus patients allowed to feed on investigator for one week	Well; positive for Rickettsiae	15
Elizaveta Gavrilovna Babalova (b 1911)	Russia	1940	*Rickettsia prowazekkii*	Self-injection with 0.5ml of brain emulsion from sick infected rat	Ill from 4 -24 days	15
Petr P. Popov (b 1889)	Russia	1949	*Rickettsia prowazekkii*	Self-infected with mite-borne typhus	Four typhus episodes	15
Roscoe Roy Spencer (1888-1982)	USA	1924	*Rickettsia rickettsii*	Vaccination with attenuated *R. rickettsii* vaccine and then exposed to rocky mountain spotted fever	Remained well	15

Table 3 continues

Table 3. Self-experimentation by doctors with bacterial pathogens between 1874 – 2022 a. *(continued)*

Medical investigator	Country	Year	Pathogen	Self-Experiment	Outcome	Ref
Viktor Mikhailovich Zhdanov (1914-1987)	Ukraine	1950	*Rickettsia*	Subcutaneous self-injection of blood from patient with rickettsial illness	Illness after 10 days	15
Jack Ralph Audy (1914-1974)	Malaysia	1947-48	*Orientia tsutsugamushi*	Mite exposure for 7 days in hyperendemic scrub typhus area; received prophylactic chloramphenicol afterwards	No infection	15
Wolfgang von Krause (1932-2012)	Germany	1969	*Candida albicans*	Swallowed a liquid of a billion *C. albicans*	Toxic febrile reaction	82
David Allen Robinson (1956-)	England	1980	*Campylobacter jejuni*	Swallowed 500 organisms added to pasteurised milk	Abdominal pain, diarrhoea	83
Simon-Leonard Dzerzhgovskii (1866-1928)	Poland	1902-09	*Corynebacterium diptheriae*	For three months self-injection 24 times with increasing doses of diptheria toxin reaching lethal doses	Mild fevers	15
Vasilii Nikolaevich Boldyrev (1872-1946)	Russia	1903	*Corynebacterium diptheriae*	For 36 days self-injection with diptheria antitoxin. Total of five lethal doses	No serious adverse effect	15
Clemens Freiherr von Pirquet (1874-1929)	Austria	1902	*Corynebacterium diptheriae*	Multiple self-injection with diptheria vaccine, and scarlet fever and tetanus vaccines	No reaction	15
Boris Iakovelvich Elbert (1890-1963)	Russia	1941	*Francisella tularensis*	Assessed resistance to repeated tularaemia infections after tularaemia vaccination and previous tularaemia infection	No serious adverse effect	15
Paul Garnault (b 1860)	France	Undated	*Mycobacterium bovis*	Sub-cutaneous insertion to forearm of piece of infected cow liver	Uncertain	15
Thomas Milton Rivers (1888-1962) [virologist]	USA	Undated	*Chlamydia psittaci*	Self-injection with live *C. psittaci* the cause of parrot fever	Uncertain	15
Anatolii Al'bertovich Shatkin (1928-1994)	Russia	1961	*Chlamydia trachomatis*	Injected *C. trachomatis* culture into his left conjunctival sac	Classical trachoma	15

Notes: a: for each specific bacterial category self-experiments are listed chronologically by year of experiment; absence of lifespan indicates dates unavailable; b: veterinarian; c: medical entomologist.

do the experiment for him, but he refused and Pettenkofer was defended by many in the medical profession who wanted to disprove Koch's views on the value of quarantine. Paradoxically, Pettenkofer requested the cholera culture material from Koch's own colleague, the bacteriologist George Gaffky (1815-1918), but experienced only a mild infection. Following a large cholera outbreak in 1892 in Hamburg, a new National Epidemic Law was proposed, and eventually passed in 1900, which legitimised contagionist policy (72). Pettenkofer's self-experiment was an effort to forestall institutionalised destruction of his life's work on public health and was a life-or-death attempt to prove his own theory. If fatal, Pettenkofer had said 'he would be dying in the service of science, like a soldier in the field of honor.' Instead, he committed suicide in 1901 (72, 86). A recent re-appraisal of his theory partly validates his approach (87). With such divergent opinions it took over forty years (1851 to 1892) and multiple International Sanitary Conferences to reach a limited accord on quarantine of ships from the East carrying cholera victims (9).

A less dramatic recognition was achieved ninety-five years later when, in 2005, the Nobel Prize in Physiology and Medicine was awarded to the Australian physician Barry Marshall (1951-) in recognition of his identification of the bacterial cause of gastritis (76). His self-experiment involved swallowing a suspension of a culture of one million *Helicobacter pylori*, leading to self-limited gastritis. He conducted the experiment in private, without his Institution's knowledge, probably reflecting institutional or social unease among scientists with self-experimentation, (88). This self-experiment was repeated by Arthur Morris (1956-) in 1987 who demonstrated persistence of the *Helicobacter pylori* infection over three years (77, 78). Four other self-experimenters received Nobel Prizes in Physiology and Medicine: Ronald Ross (1857-1932) in 1902 for his work on malaria transmission (58), Elie Metchnikoff in 1908 in recognition of his work on immunity (74); Charles Nicolle (1866-1936) in 1928 for his work on typhus (81), and Max Theiler (1899-1972) in 1951 for discovery of an effective viral vaccine against yellow fever (89).

Self-experimentation by doctors with viral pathogens after 1873

Twenty-seven self-experiments by 24 investigators across eleven countries, using ten different viruses or infectious agents, were undertaken between 1885 and 2022 (Table 4) (references 90-104). Many experimenters did not know what these infectious agents were, unlike with bacterial infections, organisms which could often be stained and seen on microscopy. One physician, Hilary Kiprowski (1916-2013), self-challenged four times with three different viruses. More than half of these experiments were testing vaccine efficacy: between 1885 and 1955 there were seven rabies vaccine self-challenges, between 1933 and 1955 six polio vaccine self-challenges, and between 1936 to 2022 five with other viral vaccines (Table 4).

All volunteers were physicians except the nurse Clara Maass (1876-1901), who was one of the two clinical investigators who died participating in yellow fever experiments in Cuba in 1901 (92, 93). At the time there was a lack of scientific evidence to prove mosquito transmission, given that some volunteers remained healthy following mosquito bites. Maass volunteered to be repeatedly bitten by *Culex fasciata* mosquitoes (now called *Aedes aegypti*) that had fed on yellow fever patients. She was the only female and American to volunteer. Dr Walter Reed (1851-1902), the American physician credited with the discovery of the vector of yellow fever transmission, agreed with these self-challenges and promoted them, but avoided doing a self-experiment himself (16). Maass considered contracting yellow fever would improve her understanding of the epidemic disease and help her to be a better nurse (93). Her death roused public sentiment, and as Dr William Lazear (1866-1900) had died the previous year following a similar self-experiment, all yellow fever experiments on human beings were stopped.

In July 1934, two groups of American researchers, each with its own immunizing agent, began human vaccinations against poliomyelitis using attenuated viruses, although questions arose on the safety and efficacy of these polio vaccines (94). Drs John Kolmer (1886-1962) and Maurice Brodie (1903-1939) both

Table 4. Self-experimentation by doctors with diseases due to viral pathogens between 1874 – 2022 [a].

Medical investigator	Country	Year	Pathogen	Self-Experiment	Outcome	Ref
James Carroll (1854-1907)	Cuba	1900	Yellow fever	Inoculation by mosquitos fed on yellow fever patients. Died later of heart damage possibly from yellow fever	Severe illness, recovered	90
William Lazear (1866-1900)	Cuba	1900	Yellow fever	Allowed mosquito fed on patients with yellow fever to continue to finish feeding on himself	Died from yellow fever	91, 92
Aristedes Agramonte y Simoni (1868-1931)	Cuba	1900	Yellow fever	Allowed self-inoculation by mosquitoes fed on patients with yellow fever	Remained well	92
Robert Cook (b 1874?)	Cuba	1900	Yellow fever	Lived in housing, slept in beds, and ate from plates of patients who died from yellow fever	No infection	15
Carlos Juan Finlay (1833-1915)	Cuba	1901	Yellow fever	Allowed self-inoculation by mosquitoes fed on patients with yellow fever	No ill effects	15
Clara Maass b (1876-1901)	Cuba	1901	Yellow fever	Allowed herself to be bitten two separate times two months apart by infected mosquitoes.	Died from yellow fever	93
Max Theiler (1899-1972)	South Africa	1936	Yellow fever	Self-injection with yellow fever vaccine and subcutaneous inoculation with tissue culture of yellow fever virus	Slight local reaction	89
René Dujarric de la Rivière (1885-1969)	France	1918	Influenza	Subcutaneous injection of filtered blood (excludes bacteria) of four patients with severe influenza	Flu-like illness	95
Takahisa Yamanouchi	Japan	1918	Influenza	Subcutaneous injection of filtered blood of influenza cases; nasal inoculation of their sputum. 52 medical professionals also volunteered.	Flu-like illness	96
Burton Bradley	Australia	1916	Dengue	Allowed bites of infected *Stegomyia* mosquitoes. Administered subcutaneous injections of infected blood	Developed dengue	97, 98
John Albert Kolmer (1886-1962)	USA	1933-34	Polio	Subcutaneous self-injection of live attenuated polio virus. Vaccine later caused polio in some children	No ill effects	15, 99
Maurice Brodie (1903-1939)	USA	1934	Polio	Self-injected formalin attenuated ground-up spinal cord of monkeys with polio; later vaccine caused polio in children	Localised inflammation	15
Albert Bruce Sabin (1906-1993)	USA	Undated	Polio	Reported self-inoculation with oral polio vaccine to test its safety when interviewed by Lawrence Altman in 1979	Not reported	16 p128
Jonas Salk (1914-1995)	USA	Undated	Polio	Self-administration of injectable polio vaccine	Not reported	16 p358

Hilary Kiprowski (1916-2013)	USA	1948	Polio	Swallowed attenuated oral polio virus vaccine	No ill effects	100
Anatolii A. Smorodintsev (1901-1986)	Russia	1955	Polio	Ingested live polio vaccine	No ill effects	15
Hilary Kiprowski (1916-2013)	USA	1949	Tick fever	Self-injection attenuated Colorado tick fever vaccine	Mild malaise	101
Emmerich Ullmann (1861-1937)	France	1885	Rabies	Self-inoculation several times with Pasteur's attenuated rabies vaccine	No ill effects	15
Iakov Iulievich Bardakh (1857-1929)	Russia	1886-87	Rabies	Self-tested own rabies vaccine before using on patients	No ill effects	15
Nikolai Fiodorovich Gamaleia	Russia	1886	Rabies	Self-tested rabies vaccine, accelerating to inclusion of overdoses	Not reported	15
Romauld Nitsch (1873-1943)	Poland	1903	Rabies	Subcutaneous injection of his own attenuated rabies vaccine	Remained well	102
Martin M. Kaplan (1915-2004)	Kenya	1955	Rabies	Self-injection with attenuated Flury rabies vaccine	Localised skin swelling	16 p116
Hilary Kiprowski (1916-2013)	Kenya USA	1955 1971	Rabies Rabies	Self-injection with attenuated Flury rabies vaccine Self-injection with Wistar rabies vaccine	Local swelling Local swelling	16 p116 15
Julio Barriera Oro (1927-2013)	Argentina	1958	Argentine haemorrhagic fever	Self-injection with a culture of the virus that caused Argentine haemorrhagic fever (O'Higgins disease)	Fever, mental, and bleeding	15
Daniel Zagury(b 1950)	France	1986	HIV	Tested a candidate AIDS vaccine made from gp160 virus coated protein by injecting into his own arm	No symptoms or toxicity	15, 103
Chuanjun Zhuo	China	2022	Covid-19	Psychiatrist who tested safety and validity of Covid-19 Sinovac vaccine, and also 15 psychiatrists on his team	Remained well	104

Notes: a: for each specific viral category self-experiments are listed chronologically by year of experiment. absence of lifespan indicates dates unavailable; b: clinical nurse.

self-challenged themselves with these attenuated polio vaccines without ill effect, although later both vaccines were shown to cause poliomyelitis in some children (99) (Table 4). The main protagonists in the development of polio vaccines at this time were Albert Sabin (1906-1993), who developed the live attenuated oral vaccine, and Jonas Salk (1914-1995), who developed a killed injectable vaccine, which is not an infectious agent. Both claimed in interviews that they had self-challenged with their own vaccines, but no published details are available of the clinical outcomes (16, 105).

Vaccination, or the use of attenuated strains (as distinguished from variolation, the earlier practice of inoculation of wild virus by scarification) was first used to prevent viral infection in the late eighteenth century when cowpox vaccination was introduced to prevent smallpox. Edward Jenner (1749-1823), who first published its benefits, did not self-challenge himself. It was not until 1885 that vaccination was further used to stimulate immunity to rabies virus in individuals bitten by rabid animals. Louis Pasteur (1822-1895), who was a chemist and not a physician, first vaccinated chickens with an attenuated cholera vaccine. Thereafter, in 1885, he vaccinated a child bitten repeatedly by a rabid dog but did not challenge himself with this vaccine. In the same year Emmerich Ullman self-tested Pasteur's vaccine,

and in 1886 two Russian doctors, Iakov Bradakh (1857-1929) and Nikolai Gamaleia self-tested a rabies vaccine before using it on patients (15). All three remained well with no ill effects (Table 4). Modern attenuated rabies vaccines in the mid-twentieth century were self-tested by Hilary Kiproski (1916-2013) and Martin Kaplan (1915-2004), who experienced only local inflammatory reactions (Table 4).

Self-testing by two doctors from France and Japan with vaccines to prevent influenza was undertaken in 1918 during the influenza epidemic following the First World War (95, 96). The viral nature of influenza was unknown at this time. A blood filtrate was used which excluded bacteria and both doctors developed a flu-like illness. In the later twentieth century other, self-injected non-infectious vaccines tested were to: dengue (97, 98), Colorado tick fever (101), Human Immune Deficiency (103), and Covid-19 (104), with a viral culture used for Argentine Haemorrhagic fever (15), (Table 4). In the publication of the results of the dengue vaccine trials in Australia the physician investigators listed themselves at the top of the participant lists, highlighting that, as the doctors who prepared the vaccine, they were the foremost of several volunteers participating in the trials (97). In a similar action a Chinese psychiatrist, Chuanjun Zhuo, as well as other psychiatrists on his team, tested the safety and validity of the Covid-19 Sinovac vaccine before proposing to evaluate it on his patients with psychosis (104). Tom Rivers, (1888-1962), described as the father of modern virology, commented that untried vaccines should first always be tested on oneself (105).

The patterns of self-experimentation

The Figure 1 illustrates patterns for different infection categories of self-experimentation in the

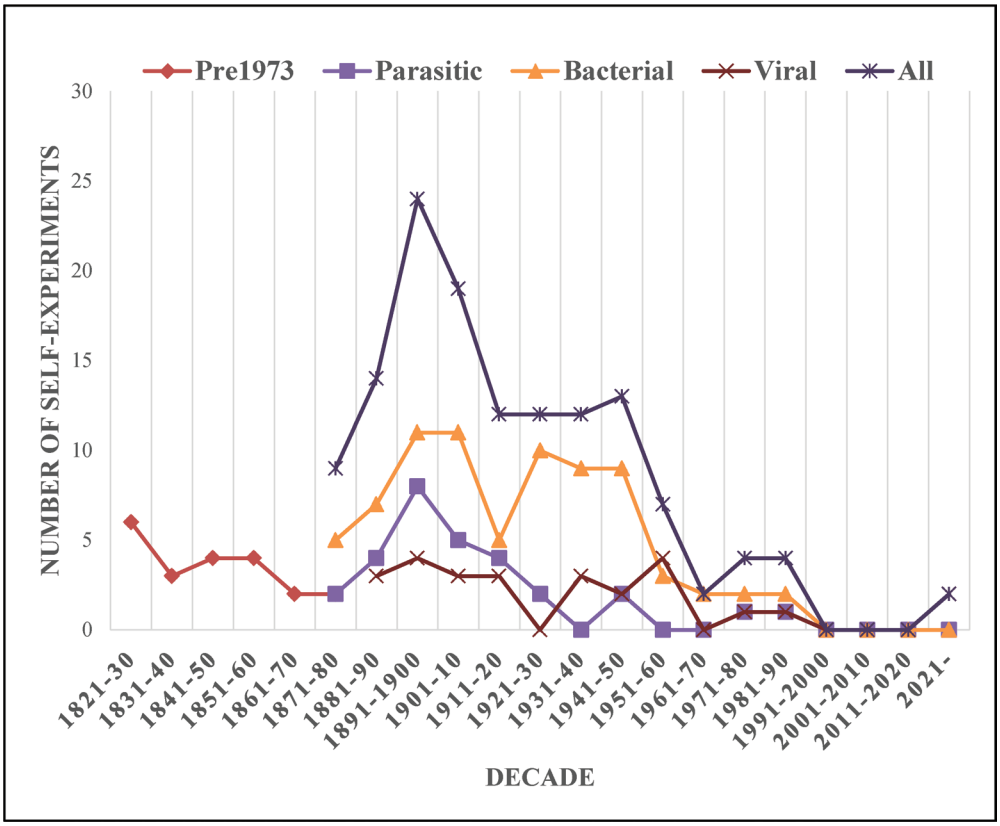

Figure 1. Decennial pattern of self-experimentation with infectious material, pathogens, or agents between 1821 to 2022. John Hunter's early experiment in 1767 is not shown.

decades between 1767 and 2022. There were 43 self-challenge studies pre-1874, and 139 after this date, 30 with parasites, 82 with bacterial pathogens, and 27 with viruses. Almost all were in men. Before 1873 the number of experiments was less than six for each decade, which corresponded to a period before contagion was established and proof that microorganisms caused disease. The early nineteenth century experiments mostly used bodily fluids, pus, or secretions in a single experiment (Table 1). Only a few later physicians experimented with multiple pathogens (Grassi, Calandruccio, Metchnikoff, Barlow, Schaudinn, Haffkine, Kiproski). There was no registry of deaths and those listed in the tables may under-report the true number. Many self-experiments with pathogenic material may have gone unreported. These investigators were nearly all apparently in good health and their reasoning for the self-experiment probably reflected the depth of their interest and commitment to understanding disease pathogenesis. There is no single characteristic of these men, whose motivations would vary from altruism to scientific curiosity, to discovery and to perseverance in seeking medical advances. Some undoubtedly were leaders in medicine.

Following this date, peak occurrence was between 1891-1900 when 25 experiments were undertaken. The time of this decennial peak was the same for bacterial, parasitic, or viral self-experiments. It corresponded to a period when infectious agents causing specific diseases were being sought, and evidence for proof of the life cycles of pathogens (eg, malaria). During World War One there was a marked fall in the number of doctors undertaking self-challenges with infectious agents, with a subsequent steady decline. Only recently, coronavirus candidate vaccines have been self-tested by medical personnel (104, 106). The last published self-experiment identified was in 2022 by Zhuo et al (Table 4). The decline in self-testing in the late twentieth century corresponded with the development of biochemical and molecular tools to characterize pathogens in patient samples, as well as the arrival of new treatments, especially vaccines. This decline also parallels the increased regulatory demands for randomized controlled trials.

Discussion

The present review comprehensively collates chronologically, and by pathogenic group, reported self-experimentation with infectious material involving live or attenuated pathogens, or infectious agents, primarily by physicians, between 1767 and 2022. Some reported cases in the foreign language literature (eg Chinese) may have been overlooked. Russian cases were thoroughly summarized by Fiks (15) and informed this review. Given that previous reports were less comprehensive, this review has been able to make more specific comparisons pre- and post-1873, to illustrate how the purpose of self- experimentation by doctors with known or unknown infectious agents changed as medical knowledge improved, becoming more informative for patient care and public health.

Before the microbiological nature of infectious disease was understood, the primary emphasis of self-challenge experiments was to investigate contagion and the relative or potential benefits of sanitary measures and quarantine. Results frequently led to conflicted opinions as findings were not definitive and were insufficiently strong to counter current beliefs. For example, in the early nineteenth century great emphasis was given by the popular physician François-Joseph-Victor Broussais (1772-1838), to copious bloodletting for inflammatory conditions which he thought had a single pathogenesis. After 1873, when specific agents of infectious disease were known, this paradigm could be challenged. Jacob Henle (1809-1885) for example, claimed diseases were caused by living agents which acted as parasites and once causal organisms were found, cures would follow (107). Self-testing at this time sought experimental evidence of disease causation, transmission, and clinical profiles. It contributed to the abandonment of phlebotomy for treatment of serious, inflammatory infections such as pneumonia (108).

Little was known about prior immunity until the twentieth century. Partly for this reason the design of self-experiments was poor and did not take account of host immunity. This is evident from the early study outcomes shown in Table 1. Cholera and yellow fever results were very inconsistent, although those for clinical outcomes of plague were more definitive. After

germ theory was established, studies became prolific during the early twentieth century. Study designs were better informed as knowledge of immunity progressed. From 1879 studies provided good evidence of parasite cycles for helminths, and for mosquito transmission of malaria (Table 2). Self-experimentation with bacterial pathogens consistently identified causative agents of several infections and their vectors. (Table 3). Later studies with viral pathogens, which tested experimental vaccines, mostly demonstrated beneficial safety profiles (Table 4).

Whether doctors should self-experiment is open to moral and ethical objections. It may be justifiable when urgent knowledge is required. The importance of making a breakthrough against the ravages of disease in the nineteenth and early twentieth century cannot be underestimated. Early self-challenge experiments must have been intended to influence changes in medical practice, due to the doctor's personal commitment to questions of major public health importance. For example, to further his initiative to control cholera and plague epidemics in India in the 1890s, Haffkine engineered a dramatic self-experiment in 1897 by giving himself triple the recommended dose of his own plague vaccine in the presence of students and the Principal of the Bombay Medical College (84). His motivation was to establish trust amongst future doctors, convince the very sceptical Indian Medical Service, and impress the people of Bombay and beyond (84). Single person self-experiments of this type, particularly by well-known medical doctors, could sway medical and public opinions, especially in the nineteenth century when communication channels for public health messages were comparatively rudimentary.

Yet was there an over-confidence and too great a self-reliance on the individual? Doctors may be better trained to observe symptoms or signs of a resulting infection, but self-experimentation is not a foolproof method. Given the sketchiness of knowledge on disease causation and pathogenesis, it remains surprising that early investigators were still willing to expose themselves to multiple risks. Perhaps they were blind to their own vulnerability, or considered there was no alternative to establishing the required knowledge. This may, at such times, have informed their perceptions of benefits outweighing risks. The mentality was arguably scientific. The body was treated as a laboratory, and seeking knowledge that would outlive speculative theories raised medicine to the status of science (109). The principle of consent, and tensions between medical paternalism and patient autonomy, were largely circumvented when experimental physicians also served as their own subjects (43)

Settling disputes in science and medicine also strongly motivated some early investigators (eg, Max Petenkkofer and Robert Koch on the virulence of *Vibrio cholera* (110); John Hunter on the nature of gonorrhoea and syphilis (111); Joseph Aureas-Turenne and Philippe Ricord on the utility of syphilisation (112); Giovanni Grassi and Salvatore Calandruccio on the priority for discovering parasite life cycles (57). The attraction of proving a key medical hypothesis, or learning how they spread, which few others believed, was enticing, but the line between egoism, recklessness and bias is easily crossed. At the time, planning experiments independent of the investigator's own interpretations was not considered necessary to reduce potential bias. At the turn of the nineteenth century Dr Walter Reed declared: 'the best justification we could offer for experimentation on others was to submit to the same risk of inoculation ourselves' (113). Reed avoided this possibility himself, possibly because advised or ordered by George Sternberg (1838-1915), US Surgeon General, not to expose himself to yellow fever infection (114), although two of his medical colleagues died following self-experimentation in pursuit of the vector of yellow fever (92). Similarly, many other celebrated pioneers in infectious disease and doctors have chosen not to expose themselves to self-challenges with infectious pathogens (eg Pasteur, Koch, Lister).

It is difficult to discern whether the later cessation of this medical practice reflected a shift in the perceived utility of self-testing or was simply due to greater reluctance amongst doctors to put themselves at risk. A doctor's personal involvement is reassuring to other participants. Prior to 1900 the practice of informed consent was non-existent although in Germany, official consent was required by the 1900s to facilitate disciplinary control (115). Today, the deliberate choice of a sample size of one would be statistically unacceptable and modern challenge studies, which test a wide range of pathogens, require large sample sizes (116).

The search for evidence drives science today, but methodological and ethical frameworks have largely negated self-experiments by doctors or other investigators, using infectious agents or other materials (117). Institutions do not usually distinguish between self-experimentation and research on subjects recruited for a specific project. However, within the guidelines of the World Medical Association Helsinki Declaration, individuals who act as their own research participants would require Ethical Committee approval (117). This protects the individual from taking unwarranted risks in the process of generating new knowledge. The principle remains to first do no harm, and doctors who self-experiment with infectious pathogens must ensure safety protections are in place, and their experiment does not predispose others to infection, or harmful side effects. Yet the practice is re-emerging with some investigators interested in accelerating Covid-19 vaccine development acting as their own subjects with non-infectious vaccines (104, 106, 118, 119). Nonetheless, it seems unlikely that the heroic efforts of earlier physicians with disease-causing organisms will be readily repeated in the modern era.

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Correspondence
Bernard John Brabin
1 Whinmoor Close, Prenton, Wirral, CH43 7XR, UK
E-mail: b.j.brabin@liverpool.ac.uk